Approved for use through 04/30/2003. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

PTO/SB/17 (10-03)

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 165

Complete if Known	
Application Number	09/856,694
Filing Date	August 13, 2001
First Named Inventor	Jan C. SIMON et al.
Examiner Name	DAVIS, Ruth A.
Art Unit	1651
Attorney Docket No.	24741-1525

METHOD OF PAYMENT (check one)

☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number: 08-1641 (Docket No. 24741-1525)

Deposit Account Name: Heller Ehrman White & McAuliffe LLP

The Commissioner is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Large Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		x		=
Independent Claims		-3** =		x		=
Multiple Dependent						=

Large Fee Code	Large Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	**Reissue independent claims over original patent
1205	18	2205	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Large Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	165
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

* Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** $165

SUBMITTED BY

Complete *(if applicable)*

Name *(Print/Type)*	Patricia D. Granados	Registration No. *(Attorney/Agent)*	33,683	Telephone	(202) 912-2000
Signature	Patricia D Granados	Date	November 3, 2003	Customer No. 26633	

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Mail Stop ___, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Jan C. SIMON *et al.*

Serial No.: 09/856,694

Filed: August 13, 2001

Art Unit: 1651

Atty Docket No.: 24741-1525

For: HYPERFORIN AS CYTOSTATIC AGENT AND HYPERFORIN OINTMENT OR CREAMS AS APPLICATION FORM

BRIEF ON APPEAL

Appeal from the Primary Examiner

Heller Ehrman
Suite 300
1666 K Street, N.W.
Washington, DC 20006

BRIEF ON APPEAL

Appellants appeal the June 6, 2003 final rejection (the "Final Rejection") of the captioned application to the Board of Patent Appeals and Interferences. Applicants filed a Notice of Appeal on September 3, 2003.

I. REAL PARTY IN INTEREST

UNIVERSITAETSKLINIKUM FREIBURG, as assignee, owns the entire right, title and interest in the captioned application and, therefore, is the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

Appellants are aware of no other appeals or interferences pertaining to the instant invention.

III. STATUS OF CLAIMS

Claims 36-54, and 56 are on appeal. These claims stand finally rejected, as indicated in the final rejection. A copy of the claims on appeal is attached.

Claims 1-19 were cancelled in a Preliminary Amendment on May 24, 2001. Claims 20-35 were cancelled in an Amendment and Response under 37 CFR §1.111 on February 21, 2002. Claim 55 was cancelled in an Amendment under 37 CFR §1.116 on August 2, 2002.

IV. STATUS OF AMENDMENTS

No amendments have been filed after the final rejection mailed on June 6, 2003.

V. SUMMARY OF THE INVENTION

The invention relates to a method for treating a condition, comprising administering to a subject in need thereof an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, wherein said condition is cancer, an inflammatory skin condition, a precancerous condition, a geriatric skin condition, or a microbial skin infection. (Specification at 7, line 15; at 9, line 31 to 10, line 12)

In one embodiment, the condition is eczema; in another, the condition is exsiccation eczemas, hyperkeratotic hand and foot eczemas, contact eczemas, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphomas, leukemia, melanoma, an epithelial pre-cancerous condition, tumor metastases, or an epithelial tumor. (Specification at 10, lines 5-11)

The subject of the treatment may be a mammal. (Specification at 10, lines 18-21)

The method of the invention may use a composition in the form of a topical ointment and the effective amount is at least 15 μg hyperforin per ml of the composition. (Specification at 7, lines 4-8) In another embodiment, the effective amount of such composition is 0.02-20 mg hyperforin per ml of the composition (Specification at 7, lines 4-11); in another, the effective amount is 1-20 mg hyperforin per ml of the composition (Specification at 7, line 13); in another, the effective amount is either at least 10 mg (Specification at 7, line 13) or at least 15 μg hypericin per ml of the composition (Specification at 7, line 20). In yet another embodiment, the effective amount of hypericin is 20-150 μg hypericin per ml of the composition. (Specification at 7, line 20)

In another embodiment, the invention is a method of treating cancer comprising administering to a subject in need thereof an effective amount of a composition consisting of hyperforin and a pharmaceutically acceptable carrier. (Specification at 5, lines 4-7) The effective amount of such composition is at least 50 μg hyperforin per ml of the composition in a form suitable for injection into a tumor. (Specification at 6, lines 34) In another embodiment, the effective amount is at least 100 μg hyperforin per μl of the composition in a form suitable for epicutaneous application. (Specification at 6, line 36) In yet another embodiment, the effective amount is at least 50 μg hyperforin per ml in plasma post-administration when administered systemically. (Specification at 7, lines 1-3) The cancer treated may be a melanoma, a lymphoma, a skin cancer, a mammary carcinoma or a leukemia carcinoma. (Specification at 5, lines 8-21) In this method of treating cancer, the hyperforin may be at least 90% pure. (Specification at 12, lines 17-18)

VI. ISSUES ON APPEAL

The issues in this appeal are:

- Whether claims 36-45 would have been obvious over The Hypericum Homepage in view of The Merck Manual within the meaning of 35 U.S.C. § 103(a).
- Whether claims 36, 38-43, 36-49 and 56 would have been obvious over Valavichyus within the meaning of 35 U.S.C. § 103(a).
- Whether claims 36, 38-54 and 56 would have been obvious over Valavichyus in view of HHP and/or DeCosterd within the meaning of 35 U.S.C. § 103(a).

VII. GROUPING OF THE CLAIMS

The rejected claims do not stand or fall together. Claims 36 and 46 are independent claims. Claim 36 recites a method of treating a condition selected from a group of conditions, with cancer being one such condition. Claim 46, on the other hand, is directed to a method of treating cancer. Thus, it is theoretically possible that a reference could anticipate claim 36 but not claim 46 by reciting one of the conditions that is not cancer. Consequently, these two claims and the claims that depend from them represent groups that do not stand or fall together.

VIII. ARGUMENT

A. Claims 36-45 would not have been rendered obvious by The Hypericum Homepage in view of The Merck Manual within the meaning of 35 U.S.C. § 103(a).

1. The Rejected Claims

Independent claim 36 recites a method for treating a condition, comprising administering to a subject in need thereof an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, wherein said condition is selected from the group consisting of cancer, an inflammatory skin condition, a precancerous condition, a geriatric skin condition, and a microbial skin infection.

Dependent claims 37-38 specify administration of the compound for treating specific conditions. Dependent claim 39 specifies the subject as a mammal. Dependent claims 40-45 prescribe that the composition be a topical ointment and that the effective amount be at least 15 micrograms of hyperforin/ml, 0.02-20 mg/ml or 1-20 mg/ml; or 15 micrograms/ml or 20-150 micrograms/ml hypericin.

2. *The PTO's Case*

The U.S. Patent and Trademark Office (the "PTO") asserts that the Hypericum Home Page ("HHP") teaches that extracts of St. John's Wort, which contains hyperforin and hypericin, exhibits anti-inflammatory and antibacterial effects when applied externally or topically and specifically teaches that hyperforin is attributed with anti-inflammatory and antibacterial effects (Final Rejection at 3). The PTO argues that although HHP does not teach a method for treating an inflammatory condition with the claimed effective amounts or for the specific conditions, it would have been obvious to one of ordinary skill in the art to use hyperforin and/or hyperforin and hypericin to treat inflammatory conditions because of the disclosed anti-inflammatory effects (Final Rejection at 4).

The PTO further argues that it would have been obvious to one of ordinary skill in the art to optimize effective volumes and concentrations as a matter of routine experimentation (Final Rejection at 4) and that it would have been obvious to one of skill in the art to include a pharmaceutical carrier.

Finally, the PTO asserts that one of ordinary skill in the art would have been motivated to use hyperforin in a method for treating inflammatory conditions with a reasonable expectation of success because of hyperforin's known benefits, as disclosed by HHP (Final Rejection at 4). The PTO cites the *Merck Manual* ("Merck") and Shroot *et al.* (U.S. Patent No. 5,151,534) and Lacefield *et al.* (U.S. Patent No. 4,021,553) as evidence that one of ordinary skill in the art would have known that eczemas are inflammatory diseases (Final Rejection at 4). According to the PTO, one of ordinary skill in the art would have been motivated to combine HHP and Merck, and utilize hyperforin in a method for treating inflammation and eczemas with a reasonable expectation of success.

3. Appellants' Response

The PTO has not presented a *prima facie* case of obviousness for several reasons. First, the PTO has the burden of proving that the relied upon disclosure in HHP was, in fact, part of the HHP website prior to Appellants' effective filing date. The PTO has not met this burden. Appellants do not repeat the arguments previously made on this issue but incorporate them by reference. (Amendment and Request for Reconsideration of March 5, 2003 at 3-4). Because the PTO has not demonstrated that HHP is prior art, the PTO's rejection is defective, as a matter of fact.

The PTO's rejection also is defective as a matter of law. Under the relevant law, the standard for assessing obviousness is (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F. 2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) The PTO has not met this burden.

St. John's Wort extract is not the same thing as hyperforin or hyperforin with hypericin. HHP discusses St. John's Wort extract. Specifically, it states that St. John's Wort contains at least ten different components. It describes some of the therapeutic uses of St. John's Wort, including the use for treating depression. It notes that it has been reported that externally applied St. John's Wort has anti-inflammatory and antibacterial effects and that such effect has been attributed to the hyperforin in the St. John's Wort extract.

It is clear from the HHP disclosure that St. John's Wort extract is a complicated combination of many different ingredients. This is supported by another reference cited by the PTO in connection with the rejection discussed below, Chavez, which states that "[t]he chemical constituents of St. John's Wort are complex, numerous and diverse" and that "[t]he

amount of the constituents is related to the harvesting period, the drying process and the storage." (Chavez at 1622) Although HHP mentions hyperforin as possibly being responsible for St. John's Wort having an anti-inflammatory property when used externally, it does not teach the use of a purified, effective amount of hyperforin in a pharmaceutical composition for use in treating any of cancer, inflammatory skin condition, a precancerous condition, a geriatric skin condition or a microbial skin infection. The PTO admits these deficiencies in HHP. It relies upon what would be "obvious to the skilled artisan" to optimize the effective amount and put it into a carrier" to complete it's case.

Appellant points out that it is not clear from HHP what type of inflammation was treated with St. John's Wort, whether it was inflammation due to a skin condition or whether there was any evidence that hyperforin was actually responsible for the anti-inflammatory response. After all, according to HHP, St. John's Wort contains at least 9 other ingredients. The PTO's primary reference is silent on these points.

In fact, the PTO has asserted that "...at the time of the claimed invention, it would have been obvious to one of ordinary skill in art to optimize effective volumes and concentration as a matter of routine experimentation" and that one "would have been motivated to use hyperforin in a method of treating anti-inflammatory conditions with a reasonable expectation of success because of its known benefit as disclosed by HHP." (Final Rejection at 4, first paragraph) However, a showing of motivation requires more than a blanket assertion of motivation without anything more. The Federal Circuit has emphasized this need in *In re San-su Lee*, 277 F. 3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002). The court stated that "...the factual showing for motivation is material to patentability, and could not be resolved on subjective belief and unknown authority." Id.

Additionally, the PTO's reliance upon Merck and the other secondary references does not cure the limitations in the HHP reference. These secondary references disclose

various types of inflammatory skin disorders, *e.g.*, eczema, lichen simplex, chronic dermatitis. The PTO asks us to assume that a treatment of inflammation of one type would be a treatment for an inflammation of another type. This simply isn't true. Even if the HHP reference disclosed the use of hyperforin in a pharmaceutical to treat inflammation from a skin disorder, (which it does not), there is no scientific reason to believe such treatment would be suitable for the specific disorders listed in claim 36 and in the rejected dependent claims. The PTO has failed to support the assumption that all substances that have anti-inflammatory properties are effective and safe for treating specific diseases that produce an anti-inflammatory response. Thus, one of skill in the art would not have an expectation of success based upon the PTO's selected combination of teachings.

B. Claims 36, 38-43, 46-49, and 56 would not have been rendered obvious over Valavichyus within the meaning of 35 U.S.C. § 103(a).

1. The Rejected claims

Claims 36 and 38-43 have been discussed above. Independent Claim 46 is directed to a method of treating cancer by administering an effective amount of a composition consisting of hyperforin and a pharmaceutically acceptable carrier. Dependent claims 47, 48 and 49 require the effective amount to be at least 50 micrograms hyperforin per ml of the composition in a form suitable for injection into a tumor, an effective amount that is at least 100 micrograms hyperforin per ml of the composition in a form suitable fro epicutaneous application, and an effective amount that is at least 50 micrograms hyperforin per ml in plasma post-administration when administered systemically, respectively. Dependent claim 56 requires the hyperforin to be at least 90% pure.

2. The PTO's Case

The PTO asserts that Valavichyus "Antitumor Activity of Medicinal Plants from the Lithuanian SSR, USSR 6, Common St. John's Wort Chamomilla Recutita" Abstract from

BIOSIS, 1986) teaches that extracts of St. John's Wort, specifically oil extracts, inhibit growth of sarcoma cells and tumor growth in animals. The PTO further asserts that it was well known in the art that oil preparations of St. John's Wort are hypericin-free and contain high concentrations of hyperforin, citing Chavez, *Monographs on Alternative Therapies in Hospital Pharmacy* 32: (12): 1621-1632 (1997) and that plant oils were used as pharmaceutical carriers (Final Rejection at 5-6).

The PTO concludes that although Valavichyus does not teach the method, volume, concentrations, mode of administration or purity of hyperforin, one of ordinary skill in the art could determine these amounts by routine experimentation. According to the PTO, one of ordinary skill in the art would have been motivated by routine practice to optimize the effective amounts of Valavichyus with a reasonable expectation for successfully treating cancer.

3. Appellants' Response

The PTO's obviousness rejection over Valavichyus is defective as a matter of fact and law. Here the PTO's error in fact relates to its interpretation of the cited art. The cited references do not disclose what the PTO claims they do. Accordingly, one could not arrive at the invention from reading Valavichyus alone or in combination with Chavez and the rejection is therefore insupportable as a matter of law.

Specifically, the entire Valavichyus abstract states:

> The effect of oil extracts of the St. John's wort-hypericum perforatum and Chamomilla recutita on the growth of sarcoma 45 and Cholangioma PC-1 was studied in rats. The administration of the extracts inhibited the growth of tumors and increased the body

weight of the animals. Data were presented on the effect of various doses of the extracts on the inhibition rate of the tumors.

It is not clear from this disclosure whether an oil extract of St. John's Wort or a combination of such extract with an oil extract of Chamomilla recutita was tested on mice tumors. Further, it is not clear what was in the oil extract of St. John's Wort. Was it only hyperforin? Or was it a combination of ingredients? How was the oil extract prepared? Was it prepared using olive oil on flowers as described in Chavez or was it prepared some other way? Appellants have shown through the references of record in this case that St. John's Wort is a complicated plant containing many different ingredients. Different extracts from different parts of the plant contain different components and these components change with time and storage. The PTO attempts to address this issue by relying upon the teachings of Chavez.

Specifically at page 1622, Chavez teaches that "typically" oil preparations of St. John's Wort are prepared by extracting the flower with olive oil. It further states that such oil preparations are hypericin free and contain lipophilic compounds, including "sufficiently high" concentrations of hyperforin. What Chavez does not teach, however, is what else is the oil extract. What are the other lipophilic compounds? Also, it is not clear what is meant by "sufficiently high concentrations" of hyperforin. It is sufficiently high for what?"

In any event, it is clear that neither of the cited references teaches nor suggests alone or in combination, a pharmaceutical composition comprising hyperforin that is 90% pure, as recited in claim 56. The PTO reads information into the cited references that is not actually there and then combines the alleged teachings to arrive at the invention. As such, the PTO's argument is based upon hindsight knowledge of the invention, which is an impermissible basis for an obviousness rejection.

As noted above, claim 46 is directed to a method of treating cancer by administering an effective amount of a composition **consisting of** hyperforin and a pharmaceutically acceptable carrier. One could not arrive at this invention by combining Valavichyus with Chavez. Nothing in either reference directs the skilled artisan to the use of hyperforin in a pharmaceutical composition to treat cancer. Nothing in either reference suggests what might be an effective amount of such composition to treat cancer. Although Valavichyus might invite experimentation in the field of the invention, such an invitation cannot be a basis for an obviousness rejection.

The PTO's obviousness case is defective for yet another reason. Claims 36 and 46 and the other claims dependent thereon recite "a pharmaceutically acceptable carrier." This claim element is not taught or suggested by the cited references. And, in view of the specification, it is improper to construe Appellant's claims to equate St. John's Wort oil or extract with "a pharmaceutically acceptable carrier."

Even if one assumes that Valavichyus suggests oil extracts generally, such extracts, without more information are not pharmaceutically effective. The science presented in the specification shows that oil extracts of St. John's Wort is undesirable. The specification shows that actual skin cells (not a culture of cells many generations removed from the reality of disease processes in humans) were studied directly. That is, when Appellants treated real skin of living humans, and then studied cell samples scraped from those subjects, the plant oil (St. John's Wort oil) failed miserably and clearly was shown to be a bad carrier. (Specification at 19, last paragraph through the middle of page 20)

Appellants have obtained data from real *in vivo* studies that shows that Valavichyus's conclusions are wrong. A skilled artisan following Valavichyus would be led in the wrong direction. To the extent Valavichyus is relevant, is shows teaching away from the claimed invention. Such evidence of leading away is a further indication of unobviousness.

Appellants reiterate that the specification provides ample information regarding the desirable aspects of pharmaceutically effective carriers. As described in the specification (see Example 11 and associated text) St. John's Wort oil is not a pharmaceutically effective carrier. In the context of Appellants' specification, which teaches how to use the claimed invention, there is no reason to think that plant oils *per se* somehow are pharmaceutically acceptable carriers. On the contrary, the oil studied (St. John's Wort) was not acceptable and it was found that the active ingredients can be combined with ethanol and cream, as described on page 6 first paragraph, ethanol and greasy ointment base (second paragraph of page 6). Ethanol is particularly useful for the pharmaceutically effective carrier (page 8, second paragraph) and "plant extracts" such as plant oils, if used, are used as ingredients, not carriers *per se*, as mentioned on page 8 lines 19-22. Crude plant oil extracts generally are not pharmaceutically acceptable. The specification at pages 8 and 9 describes carriers that are acceptable. Plant oil extracts are not in this list.

The PTO's assumption that "[i]t was also known in the art that plant oils were used as pharmaceutical carriers" (Final Rejection at 5) is simply not correct. A pharmaceutically acceptable carrier is not a plant oil extract. In fact, as discussed above, the specification provides data showing that a plant oil extract studied was not acceptable and that the plant oil has to be blended with acceptable materials (Specification at page 9, first three full paragraphs and Example 11).

Appellants further maintain that the above discussed data in the specification bolster the non-obviousness of their invention. Even if the PTO had presented a *prima facie* case of obviousness, the evidence presented in the specification would rebut such case. The specification teaches "pharmaceutically acceptable" carriers such as "ointment or cream" as, for example, stated on page 10, line 37. Particular advantages of this acceptable carrier are also stated on the bottom of page 37. The effects of the ointment and creams

(representative pharmaceutically acceptable carriers) "is superior to that of the known St. John's Wort oil" as stated on page 11 lines 9 to 10 of the specification. This effect was previously generally unknown and unexpected. Another effect is that "penetration of active compounds" from these particular pharmaceutically acceptable carriers "is superior to that of active compounds from oils." Applicants note in this context that the word "oils" includes plant oils such as plant oil extracts. Such plant oil preparations are NOT included within the group of pharmaceutically acceptable carriers, as is stated above.

Here, Appellants discovered to their surprise through investigation that the St. John's Wort ointment (i.e. with a pharmaceutically effective carrier) "brings about an inhibition of proliferation (of epidermal cells) . On the other hand, the use of St. John's Wort oil results in an increase in proliferation" as seen in the data of Figure 5 from the specification (see page 20 lines 14-18). Clearly, the claimed compositions (not with the plant oil as carrier but with an acceptable carrier) exhibited highly beneficial activity as unexpected results in comparison with the "natural" product promoted and taught by Valavichyus (and HHP.) These unexpected results are strong evidence of unobviousness.

C. Claims 36, 38-54 and 56 would not have been obvious over Valavichyus in view of HHP and/or DeCosterd within the meaning of 35 U.S.C. § 103(a).

1. The Rejected Claims

Claims 36 to 49 have been discussed above. Claims 50-54 depend from claim 46 and further limit the type of cancer being treated. These cancers are melanoma, lymphoma, skin cancer, mammary carcinoma, and leukemia carcinoma.

2. The PTO's Case

The PTO rejects all the claims as being obvious over Valavichyus in view of HHP or DeCosterd, the secondary references being cited for allegedly teaching that extracts of St. John's Wort have anti-tumor properties. Specifically, the PTO states that "DeCosterd teaches extracts of Hypericum inhibit growth of colon carcinomas" and further teaches derivatives of hyperforin exhibit the growth-inhibiting activity (Final Rejection at 8). From this the PTO concludes that at the time of the invention, hyperforin, derivatives thereof and extracts of Hypericum were well known as effective agents against cancer of various kinds.

3. Appellants' Response

Appellants respond to this rejection by arguing that nothing in DeCosterd cures the deficiencies in the PTO's case, as set forth above in connection with the discussion of HHP and Valavichyus. DeCosterd teaches the isolation of two new compounds, hyperevolutin A and hyperevolutin B from the root bark of Hypericum revolutin VAHL. These compounds showed growth inhibitory activity against *in vitro* colon carcinoma cell line. Such a report does not direct the skilled artisan to Appellants' invention. Rather, it invites experimentation and further investigation. As such, it does not support an obviousness rejection.

VIII. CONCLUSION

It is respectfully requested that the Board pass the presently rejected claims on to allowance.

Respectfully submitted,

Date November 3, 2003

By Patricia D. Granados
Patricia D. Granados
Registration No. 33,683

Customer No. 26633

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, DC 20006
(202) 912-2000 (telephone)
(202) 912-2020 (facsimile)

Appendix - Claims on Appeal

36. A method for treating a condition, comprising administering to a subject in need thereof an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, wherein said condition is selected from the group consisting of cancer, an inflammatory skin condition, a precancerous condition, a geriatric skin condition, and a microbial skin infection.

37. The method according to claim 36, wherein the condition is eczema.

38. The method according to claim 36, wherein said condition is selected from the group consisting of exsiccation eczemas, hyperkeratotic hand and foot eczemas, contact eczemas, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphomas, leukemia, melanoma, an epithelial pre-cancerous condition, tumor metastases, and epithelial tumor.

39. The method according to claim 36, wherein said subject is a mammal.

40. The method according to claim 36, wherein said composition is in the form of a topical ointment and said effective amount consists of at least 15 μg hyperforin per ml of the composition.

41. The method according to claim 36, wherein said composition is in the form of a topical ointment and said effective amount is 0.02-20 mg hyperforin per ml of the composition.

42. The method according to claim 41 wherein said effective amount is 1-20 mg hyperforin per ml of the composition.

43. The method according to claim 42 wherein said effective amount is 10 mg hyperforin per ml of the composition.

44 The method according to claim 36, wherein said effective amount is at least 15 μg hypericin per ml of the composition.

45. The method according to claim 36, wherein said effective amount of hypericin is 20-150 μg hypericin per ml of the composition.

46. A method of treating cancer comprising administering to a subject in need thereof an effective amount of a composition consisting of hyperforin and a pharmaceutically acceptable carrier.

47 The method according to claim 46, wherein said effective amount is at least 50 μg hyperforin per ml of the composition in a form suitable for injection into a tumor.

48. The method according to claim 46, wherein said effective amount is at least 100 μg hyperforin per μl of the composition in a form suitable for epicutaneous application.

49. The method according to claim 46, wherein said effective amount is at least 50 μg hyperforin per ml in plasma post-administration when administered systemically.

50. The method of claim 46, wherein said cancer is a melanoma.

51. The method of claim 46, wherein said cancer is a lymphoma.

52. The method of claim 46, wherein said cancer is a skin cancer.

53. The method of claim 46, wherein said cancer is mammary carcinoma.

54. The method of claim 46, wherein said cancer is leukemia carcinoma.

56. The method of claim 46, wherein said hyperforin is at least 90% pure.